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(54) TRIFLUOROMETHYLIMIDAZOLES USEFUL AS ANTI-GOUT AGENTS

(71) We, MERCK & CO. INC., a corporation duly organised and existing under the laws of the State of New Jersey, United States of America, of Rahway, New Jersey, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

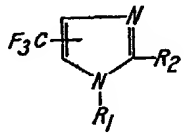
Gout is a condition affecting humans and lower animals, particularly birds and reptiles. It is characterized by perversion of the purine metabolism resulting in an excess of uric acid in the blood, by attacks of acute arthritis, and by formation of chalky deposits in the cartilages of the joints. These deposits are made up chiefly of urates, or uric acid. Hyperuricemia is a condition characterized by an excess of uric acid in the blood.

Uric acid serves no biochemical function in the body and is merely an end product of purine metabolism. It is well known that the purine bases adenine and guanine, which play key roles in a wide variety of chemical processes, both give rise to uric acid in the body. Adenylic acid and guanylic acid are converted to the free purine bases by destructive metabolic enzymes. A portion of the free purine bases is converted to purine ribonucleotides and the remainder is degraded to the free bases xanthine and hypoxanthine. A single enzyme, xanthine oxidase, converts both xanthine and hypoxanthine to uric acid for excretion.

Although human purine biosynthesis can be inhibited at the stage of formyl glycinimide ribotide by the glutamine antagonists azaserine and 6 - diazo - 5 - oxo - 1 - norleucine, a high incidence of undesirable side effects precludes their being used clinically for this purpose. In recent years, substantial progress has been made in attempting to control the excessive levels of uric acid in patients afflicted with gout through the use of pharmaceutical agents. Uric acid synthesis has been effectively blocked by the use of allopurinol, 4 - hydroxypyrazolo - [3,4 - d] - pyrimidine, a compound which is a structural isomer of hypoxanthine. Allopurinol acts as a specific inhibitor of the enzyme xanthine oxidase, which is responsible for the conversion of both hypoxanthine and xanthine to uric acid. As a direct result of the administration of this compound to patients afflicted with gout, part of the uric acid which would normally end up in the urine is replaced instead by the oxypurines, hypoxanthine and xanthine, thus greatly reducing the content of uric acid in serum and urine. Azathioprine has also been used in patients afflicted by gout to inhibit the excessive purine synthesis, which tends to produce abnormal amounts of uric acid. Other compounds, such as acetylsalicylic acid, thiophenylpyrazolidine, and phenylbutazone have been used

in the treatment of gout. Many of the existing compounds used in the treatment of gout, however, relieve the inflammation and other symptoms connected therewith but have no effect on the conditions which give rise to gouty arthritis or hyperuricemia. Thus, there is still a need for compounds that can be used in the prophylactic treatment of gout as well as for the treatment of other abnormal conditions associated with hyperuricemia.

In accordance with the present invention, there are provided novel imidazoles having the general formula



(I)

in which R_1 is a hydrogen atom or a C_{1-5} alkyl or C_{1-5} hydroxyalkyl radical, e.g. methyl, ethyl, butyl, 2-hydroxyethyl or 3-hydroxypropyl; and R_2 is a hydrogen atom, a C_{1-5} alkyl radical, such as methyl, ethyl or propyl, an aryl or heteroaryl radical, such as phenyl, naphthyl, quinolyl, cinnolyl or a 5-membered or 6-membered heteroaryl ring system containing 1 to 3 hetero atoms selected from oxygen, nitrogen, and sulfur, e.g. pyrazinyl, thienyl, furyl, thiazolyl or pyridyl, said aryl or heteroaryl radical optionally having from one or three C_{1-5} alkyl or C_{1-5} alkoxy substituents, a substituted phenyl radical having from one to three of the following substituents, viz. halogen (i.e. fluorine, bromine, chlorine or iodine), cyano, carboxy, (C_{1-5} alkoxy)carbonyl, e.g. methoxycarbonyl, ethoxycarbonyl or butoxycarbonyl, C_{1-5} alkyl, e.g. methyl, ethyl, propyl, butyl, isopropyl or pentyl, C_{2-5} alkylidene, e.g. ethylidene, propylidene, butylidene or pentylidene, sulfamoyl, C_{1-5} alkylsulfamoyl, di(C_{1-5} alkyl)sulfamoyl, e.g. dimethylsulfamoyl, ethylsulfamoyl or butylsulfamoyl, C_{1-5} alkoxy, e.g. methoxy, ethoxy or butoxy, C_{2-5} alkanoylamino, e.g. acetylamino, propionylamino or butyrylamino, nitro, amino, C_{1-5} alkylamino, e.g. methylamino, ethylamino or propylamino, di(C_{1-5} alkyl)amino, e.g. dimethylamino, diethylamino or dibutylamino, methylenedioxy joined to adjacent carbons of the phenyl ring, e.g. 3,4-methylenedioxy, a fused alkylene bridge containing from 3 to 6 carbons, e.g. a propylene (preferably 3,4-propylene), butylene, or pentylene bridge, and joined to adjacent carbon atoms of the phenyl ring, or a β-carboxy-acrylamido group, viz. —NHCOCH=CHCOOH; and pharmaceutically acceptable salts thereof.

4(5)-Trifluoromethylimidazoles of the above formula have been found to be effective anti-gout and anti-hyperuricemic agents in that they will inhibit the action of the enzyme xanthine oxidase and thus reduce the content of uric acid in serum and urine. In addition, some of the 4(5)-trifluoromethylimidazoles exhibit diuretic and hypotensive activity and will inhibit gastric secretion.

The salts within the scope of the invention are the non-toxic pharmaceutically acceptable quaternary salts such as the methiodides and ethiodides when the heterocyclic group in the 2-position contains a nitrogen atom, alkali metal and alkaline-earth metal salts, such as the sodium, potassium and calcium salts, and those mineral acid salts such as the hydrochloride salts, when the substituent in the 2 position is a heterocyclic ring containing at least one nitrogen atom, such as a pyridine ring.

These compounds in which R_1 in Formula I is hydrogen, C_{1-5} alkyl or C_{1-5} hydroxyalkyl, and R_2 is naphthyl, pyridyl, alkyl, quinolyl, thiazolyl, furyl, thienyl, cinnolyl, pyrazinyl or substituted phenyl in which the substituent is halo, cyano, carboxy, alkoxy carbonyl, C_{1-5} alkyl, sulfamoyl, C_{1-5} alkoxy, C_{2-5} alkanoylamino, nitro, amino, C_{1-5} monoalkylamino, di C_{1-5}(alkyl)amino, methylenedioxy, a fused alkylene bridge, or the β-carboxy-acrylamido group, represent a preferred sub-class of compounds falling within the scope of the present invention.

It should be understood that the 1-unsubstituted trifluoromethylimidazoles discussed herein are compounds in which the trifluoromethyl substituent is at either the 4 or 5 position in the imidazole ring. The hydrogen atom on a nitrogen in the imidazole ring is in a state of tautomeric equilibrium, with the result that the 4 or 5 positions are equivalent.

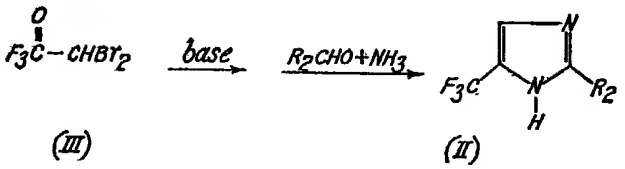
Typical of the compounds falling within the definition of Formula I are:

2 - (4 - pyridyl) - 4(5) - trifluoromethylimidazole
1 - methyl - 2 - (4 - pyridyl) - 4 - trifluoromethylimidazole
2 - (4 - thiazolyl) - 4(5) - trifluoromethylimidazole
2 - (2 - furyl) - 4(5) - trifluoromethylimidazole

1 - ethyl - 2 - (4 - thiazolyl) - 4 - trifluoromethylimidazole
2 - isopropyl - 4(5) - trifluoromethylimidazole
2 - phenyl - 4(5) - trifluoromethylimidazole
2 - (*o* - cyanophenyl) - 4(5) - trifluoromethylimidazole
2 - (*p* - ethylphenyl) - 4(5) - trifluoromethylimidazole
1 - propyl - 2 - phenyl - 4 - trifluoromethylimidazole
2 - vinylphenyl - 4(5) - trifluoromethylimidazole
2 - (*p* - sulfamoylphenyl) - 4(5) - trifluoromethylimidazole
2 - (*p* - N - methylsulfamoyl) - 4(5) - trifluoromethylimidazole
1 - methyl - 2 - (*p* - sulfamoylphenyl) - 4 - trifluoromethylimidazole
1 - methyl - 2 - phenyl - 5 - trifluoromethylimidazole
2 - (*p* - methoxyphenyl) - 4(5) - trifluoromethylimidazole
2 - (6 - quinolyl)- 4(5) - trifluoromethylimidazole
2 - (3 - furyl) - 4(5) - trifluoromethylimidazole
2 - (2 - thienyl) - 4(5) - trifluoromethylimidazole
2 - (3,4 - methylenedioxyphenyl) - 4(5) - trifluoromethylimidazole
2 - (*o* - methoxyphenyl) - 4(5) - trifluoromethylimidazole
2 - (*p* - acetylaminophenyl) - 4(5) - trifluoromethylimidazole
2 - (*p* - cyanophenyl) - 4(5) - trifluoromethylimidazole
1 - methyl - 2 - (*p* - methoxyphenyl) - 4 - trifluoromethylimidazole
1 - methyl - 2 - (*p* - methoxyphenyl) - 5 - trifluoromethylimidazole
2 - (*p* -dimethylaminophenyl) - 4(5) - trifluoromethylimidazole
2 - (5 - indanyl) - 4(5) - trifluoromethylimidazole
2 - (1 - naphthyl) - 4(5) - trifluoromethylimidazole
2 - (3,4 - dichlorophenyl) - 4(5) - trifluoromethylimidazole
2 - (*m* - chlorophenyl) - 4(5) - trifluoromethylimidazole
2 - (*p* - fluorophenyl) - 4(5) - trifluoromethylimidazole
1 - methyl - 2 - (*p* - chlorophenyl) - 4 - trifluoromethylimidazole
2 - (*p* - carboxyphenyl) - 4(5) - trifluoromethylimidazole
2 - (3 - cinnolyl) - 4(5) - trifluoromethylimidazole
2 - (2 - naphthyl) - 4(5) - trifluoromethylimidazole,
1 - methyl - 2 - (*p* - acetylaminophenyl) - 4 - trifluoromethylimidazole, and
1 - (2 - hydroxyethyl) - 2 - (1 - naphthyl) - 4(5) - trifluoromethylimidazole.

The compounds of the present invention in which R_1 is hydrogen and R_2 is other than an amino-substituted phenyl residue can be prepared by first reacting a 1,1 - dihalo - 3,3,3 - trifluoroacetone compound, such as 1,1 - dibromo - 3,3,3 - trifluoroacetone, with a base, such as sodium acetate, aqueous ammonia or potassium carbonate, and then reacting the basic mixture with the appropriate carboxaldehyde and ammonia. The carboxaldehyde may be an alkyl carboxaldehyde, such as acetaldehyde or propionaldehyde, an arylcarboxaldehyde, such as benzenecarboxaldehyde, a substituted arylcarboxaldehyde, such as *o*-cyanobenzenecarboxaldehyde, *p*-nitrobenzenecarboxaldehyde, *p*-sulfamoylbenzenecarboxaldehyde, and *p*-methoxybenzenecarboxaldehyde, or a heteroarylcarboxaldehyde, such as pyridinecarboxaldehyde, quinolinecarboxaldehyde, thiazolecarboxaldehyde, thiophenecarboxaldehyde, or cinnolinecarboxaldehyde.

The overall reaction scheme can be depicted as follows:



(III) (II)

For example, where R_2 in Formula II is 4-pyridyl, the trifluoromethylimidazole compound is prepared by reacting about equimolar amounts of, for example, 1,1 - dibromo - 3,3,3 - trifluoroacetone with 4-pyridinecarboxaldehyde and ammonia. In general, the trifluoroacetone compound is first added to a solution containing a slight excess of a mild base; any mild base, such as sodium acetate or potassium carbonate, may be used. Hydroxylic solvents such as aqueous ethanol or water may be used, but the reaction is generally carried out in water. The solution is heated for from about 5 minutes to about 2 hours at a temperature between room temperature and about 150°C.; the preferred temperature range, however, is about 80—100°C. The reaction is then

cooled, preferably to ice bath temperatures. The cooled solution is then added to a solution of the carboxaldehyde in a suitable solvent. Water-miscible solvents such as methanol, ethanol, dioxane or tetrahydrofuran may be used. Ammonia is then added to the reaction mixture, and the mixture is allowed to stand at about room temperature for from about 1—10 hours. The ammonia may be added as a gas or alternatively as an aqueous or alcoholic solution. The trifluoromethylimidazole compound is then obtained by known techniques. For example, concentration of the reaction mixture will generally yield the trifluoromethylimidazole compound as a solid residue. The product can be purified by recrystallization from an appropriate solvent such as water, acetonitrile or benzenehexane.

Those compounds in which the substituent on the phenyl ring is amino can be prepared from the 2-phenyltrifluoromethylimidazole compounds having a C_{2-3} alkanoylamino group as the substituent on the phenyl ring. The reaction is carried out by first suspending a C_{2-3} alkanoylaminophenyltrifluoromethylimidazole compound such as, for example, 2 - (*p* - acetylaminophenyl) - 4(5) - trifluoromethylimidazole, in a dilute mineral acid such as, for example, 10% hydrochloric acid, and heating the acid suspension for from about 15 minutes to about two hours at a temperature of about 50—150°C. The preferred temperature range is 75—100°C. The aminophenyltrifluoromethylimidazole compound is obtained by neutralizing the acid solution with a mild alkali such as sodium bicarbonate and collecting the resulting precipitate by known techniques. Alternatively, the 2-aminophenyltrifluoromethylimidazole compounds can be obtained by catalytic reduction of the corresponding nitro compounds.

Those compounds in which the substituent in the 2-position is the residue formed by reaction of a cyclic anhydride with an amine can be prepared from a 2 aminophenyl-4(5)-trifluoromethylimidazole by reacting the 2-aminophenyl - 4(5) - trifluoromethylimidazole compound with maleic anhydride in a suitable solvent, for example, diethyl ether. The reaction is generally carried out at room temperature, but temperatures between room temperature and about 50°C. are suitable. The reaction product generally crystallizes from the reaction mixture and is collected and purified by known techniques.

The compounds of Formula I in which R_1 is C_{1-3} alkyl can be prepared by reacting a 4(5)-trifluoromethylimidazole, for example, 2 - (*p* - fluorophenyl) - 4(5) - trifluoromethylimidazole, with an alkylating agent such as diazomethane or with a C_{1-3} alkyl sulfate such as dimethyl sulfate. The reaction is carried out in a suitable solvent such as acetic acid or methanol. The alkylation may be carried out at room temperature, but it is preferred to carry out the reaction at elevated temperatures from about 50°—150°C. for from about 1—30 hours. The reflux temperature of the solvent is a convenient temperature for the alkylation step. The alkylated trifluoromethylimidazole compound is then isolated by known techniques. One isolation method, for example is to remove the solvent and triturate the residue with dilute alkali, such as ammonium hydroxide, and take up the product in a suitable solvent, such as hexane. The alkylated trifluoromethylimidazole compound is then obtained upon removal of the solvent.

Those compounds of Formula I in which R_1 is C_{2-3} hydroxyalkyl can be prepared by reacting a C_{2-3} 1,2-epoxy or 1,3-epoxyalkane, for example, 1,2-epoxyethane or 1,3-epoxypropane, with about an equimolar mixture of a 4(5)-trifluoromethylimidazole compound and a Lewis acid, in a suitable solvent, such as acetic acid or methyl alcohol. As the Lewis acid, compounds such as boron trifluoride and sulfur trioxide can be used. Generally, a molar excess of the epoxide is used, and the reaction is carried out at a temperature between about −40°C. and 60°C. The preferred reaction temperature, however, is between about 20°C. and 50°C. The epoxide is usually added gradually at such a rate as to keep the reaction within the desired temperature range. Depending upon the temperature range, the reaction mixture is allowed to stand for from about 10 minutes to about 18 hours. The hydroxy-alkylated 4(5)-trifluoromethylimidazole compound is then isolated by known techniques.

In order to prepare those compounds of Formula I in which R_1 is hydroxyalkyl, it may be necessary in some instances to protect the compounds having substituents which are sensitive to the alkylating agents in order to obtain a good yield. Where the substituent in the 2- position is a pyridyl ring, the pyridyl ring can be protected by converting it to an N-oxide, which is then converted to the free pyridyl group after alkylation by conventional means. Where the substituent on the 2-phenyl substituent is a carboxy group, the carboxy group can be protected by converting it to the ester. Where the phenyl substituent is substituted with an amino group or a monoalkylamino group, the amine function can be protected by acylation with, for example, an acetyl group. Where the substituent on the 2-phenyl substituent is a disubstituted amino

group, it can be protected by converting it to an N-oxide. Where the substituent on the 2-phenyl substituent is a sulfamoyl group, the sulfamoyl group may also be alkylated. The sufamoyl group can be regenerated by reaction with chlorosulfonic acid, followed by reaction of the resulting sulfonyl chloride compound with ammonia. In those cases where a protecting group is necessary, the protecting group is removed by known techniques.

The quaternary salts that fall within the scope of the present invention have as the substituent in the 2- position a nitrogen-containing aromatic ring such as a pyridine or quinoline ring. These quaternary salts can be prepared by reacting the 2- substituted 4(5)-trifluoromethylimidazole compound with an alkyl iodide for example, methyl iodide or ethyl iodide in a suitable solvent, such as methanol, ethanol, or dimethylformamide. The reaction is generally carried out at room temperature, and the quaternary salt is usually obtained as a solid upon removal of the solvent. The following are examples of quaternary salts within the scope of the present invention:

N - methyl - 4 - [4(5) - trifluoromethyl - 2 - imidazolyl] pyridinium iodide
N - ethyl - 4 - [4 - (5) - trifluoromethyl - 2 - imidazolyl] quinolinium iodide
N - methyl - 2 - (1 - ethyl - 4 - trifluoromethyl - 2 - imidazolyl)pyridinium iodide, and
N - methyi - 3 - [1 - (2 - hydroxyethyl - 4 - trifluoromethyl - 2 - imidazolyl)] pyridinium iodide.

The metal salts of the 4(5)-trifluoromethylimidazoles, that is, those compounds where R_1 in Formula I is hydrogen, can be prepared by known methods. For example, the sodium or potassium salt can be prepared by addition of an equivalent amount of sodium or potassium hydroxide to a solution of the trifluoromethylimidazole compound. The salt is then obtained by concentrating the reaction mixture.

The acid addition salts of the 4(5)-trifluoromethylimidazoles having in the 2-position a heterocyclic ring containing at least one nitrogen atom can be prepared by any of the known methods for preparing acid addition salts of amines.

4(5)-Trifluoromethylimidazoles of this invention have been found to inhibit the action of the enzyme xanthine oxidase, resulting in a significant decrease in the concentration of uric acid in the blood and urine and thus aborting attacks of gout.

In addition, some of the 4(5)-trifluoromethylimidazoles, such as 2-(2-pyridyl)-4(5)-trifluoromethylimidazole and 2-(4-pyridyl)-4(5)-trifluoromethylimidazole, have been found to exhibit diuretic and hypotensive activity and to inhibit gastric secretion.

For testing purposes, xanthine oxidase obtained from milk may be used to demonstrate the ability of the 4(5)-trifluoromethylimidazoles to inhibit the enzyme. The general procedure is to use a 5—10 unit suspension of the enzyme per milliliter of 60% saturated ammonium sulfate; 1 unit of such a suspension converts 1μ mole of xanthine to uric acid per minute. Generally, for a 1-day assay, about 0.05 ml. of enzyme is diluted with about 3 ml. of buffer. As the buffer, tris buffer (bromethamine) (0.05 mole) pH 7.4 may be used. The inhibitor to be tested is dissolved in buffer or a suitable solvent, such as dimethylsulfoxide; the same solvent is used to dilute the solution. The buffer, hypoxanthine and solvent are placed in a cell, and the resulting solution is shaken to absorb air. The diluted enzyme solution is then added, and the rate of increase in absorbance at 290 mμ is noted with a recording spectrophotometer. Generally, sufficient enzyme is used to give about 0.1 absorbance units change per minute, and sufficient inhibitor is used to give 30—70% inhibition. The μM concentration of inhibitor necessary for 50% inhibition ($V_0/V_1=2$) is determined by plotting V_0/V_1 against I, where V_0=velocity without inhibitor, V_1=velocity with inhibitor, and I=inhibitor concentration. The activity of the tested compound is expressed in terms of percent inhibition.

The therapeutically active trifluoromethylimidazoles can be administered as the active ingredient in association with a pharmaceutically acceptable carrier. Such compositions may be in the form of tablets, elixirs syrups, pills and capsules. These preparations may be made by any of the known pharmaceutical methods. For example, in tablet form, they are compounded with an inert pharmaceutical carrier which may contain a suitable binder, for example, gums, starches, and sugars. They may also be incorporated into a gelatin capsule or formulated into elixirs which have the advantage of being susceptible to manipulations in flavor by the addition of standard natural or synthetic flavoring materials. The compound is generally administered in compositions which are so proportioned as to afford a unit dosage of about 30 mg. to 1.5 gm. per day. The preferred dosage level, however, is about 100—800 mg. per day.

The following examples of Formulations, in which mesh and capsule sizes are U.S. standards, serve to illustrate typical tablet, capsule, and elixir formulations incorporating the therapeutically active 4(5)-trifluoromethylimidazoles of this invention:

FORMULATION I:

Compressed Tablet Comprising 0.5 GM. of Active Ingredient

Ingredient	Amount—Mg.
2-(4-pyridyl)-4(5)-trifluoromethylimidazole	500.0
Starch paste — 12½%, 100 cc. allow.	12.5
	512.5
Starch, U.S.P. Corn	25.0
Magnesium stearate	5.5
	543.0

The 2 - (4 - pyridyl) - 4(5) - trifluoromethylimidazole is granulated with the starch paste and while moist passed through a No. 14 screen, dried at 45°C. for 20 hours, and then passed 3 times through a No. 14 screen. The starch is then passed through a No. 90 bolting cloth onto the granulation, and all ingredients are blended thoroughly. The magnesium stearate is passed through a No. 90 bolting cloth onto the granulation, and these ingredients are blended, after which the granulation is compressed into tablets using a 14/32" flat, bevelled, scored punch having a thickness of 0.205± 0.005" yielding 1,000 tablets each weighing 0.543 grams.

FORMULATION II:

Encapsulation — For 250 MG. Capsule

Ingredient	Amount — Mg.
2-(6-quinolyl)-4(5)-trifluoromethyl-imidazole	250
Lactose	93
Talc	7

Blend lactose, talc and the 2 - (6 - quinolyl) - 4(5) - trifluoromethylimidazole in suitable blending equipment, and encapsulate into a No. 2 capsule at a target weight of 350 mg.

FORMULATION III:

Liquid Suspension — Formula

Ingredient	Amount — g./l.
Veegum H.V.	3.0
Water	150.0
Methyl Paraben	1.0
2-(*p*-carboxyphenyl)-4(5)-trifluoromethyl-imidazole	50.0
Kaolin	10.0
Flavor	1.0
Glycerin, 9.5 to 1 liter	

Suspend Veegum in water with vigorous agitation, add methyl paraben and allow to stand overnight to ensure complete hydration of Veegum. In separate vessel suspend 2 - (*p* - carboxyphenyl) - 4(5) - trifluoromethylimidazole in about 750 cc. of glycerol. Add kaolin and stir until homogeneous. Slowly add aqueous dispersion of Veegum and methyl paraben. Add flavor and continue agitation for 1 hour to ensure homogeneity. Q.S. with remaining glycerin to 1:1. Stir until homogeneous. 1 Teaspoonful contains 250 mg. of 2 - (*p* - carboxyphenyl) - 4(5) - trifluoromethyl-imidazole.

The following examples are given for purposes of illustration and not by way of limitation of the invention.

Example 1

2 - (4 - Pyridyl) - 4(5) - Trifluoromethylimidazole

Sodium acetate trihydrate (11.6 grams, 0.084 mole) is dissolved in 40 ml. of water, and 1,1 - dibromo - 3,3,3 - trifluoroacetone (11.6 grams, 0.042 mole) is added to the resulting aqueous solution. The solution is heated for 30 minutes at 100°C. and is then cooled in an ice bath. The cooled solution is added to a solution of 4-pyridine-carboxaldehyde (4.7 grams, 0.044 mole) in methanol (200 ml.). Concentrated aqueous ammonia (50 ml.) is added to the alcoholic solution, and the reaction mixture is allowed to stand for 5 hours at room temperature. The mixture is then concentrated to about 75 ml., and the product separates from the solution as an oil which solidifies on standing. Upon recrystallization from water, there is obtained 2 - (4 - pyridyl) - 4(5) - trifluoromethylimidazole, m.p. 156—157.5°C.

When in the above procedure 3-pyridinecarboxaldehyde is used in place of 4-pyridinecarboxaldehyde, there is obtained 2 - (3- pyridyl) - 4(5) - trifluoromethyl-imidazole, m.p. 228—228.5°C.

When in the above procedure 2-pyridinecarboxaldehyde is used in place of 4-pyridinecarboxaldehyde, there is obtained 2 - (2 - pyridyl) - 4(5) - trifluoromethyl-imidazole, m.p. 156—157.5°C.

The procedure described in Example 1 is used to prepare the following compounds (Examples 2—33A):

Examples 2 — 33A

Ex. No.	(0.044 mole) Starting Material	Product	Melting Point
2	2-quinoline-carboxaldehyde	2-(2-quinolyl)-4(5)-trifluoromethylimidazole	156.5—158°C.
3	4-thiazole-carboxaldehyde	2-(4-thiazolyl)-4(5)-trifluoromethylimidazole	235—236°C.
4	2-furan-carboxaldehyde	2-(2-furyl-4(5)-trifluoromethylimidazole	192—193.5°C.
5	isobutyraldehyde	2-isopropyl-4(5)-trifluoromethylimidazole	201.5—202.5°C.
6	propionaldehyde	2-ethyl-4(5)-trifluoromethylimidazole	115—122°C.
7	acetaldehyde	2-methyl-4(5)-trifluoromethylimidazole	161—165°C.
8	formaldehyde	4(5)-trifluoromethylimidazole	148.5—149.5°C.
9	1-naphthylene-carboxaldehyde	2-(1-naphthyl)-4(5)-trifluoromethylimidazole	249—250°C.
10	2-naphthylene-carboxaldehyde	2-(2-naphthyl)-4(5)-trifluoromethylimidazole	210—211°C.
11	2-thiophene-carboxaldehyde	2-(2-thienyl)-4(5)-trifluoromethylimidazole	211.5—212°C.
12	*p*-cyanobenzaldehyde	2-(*p*-cyanophenyl)-4(5)-trifluoromethylimidazole	207—208°C
13	*p*-fluorobenzaldehyde	2-(*p*-fluorophenyl)-4(5)-trifluoromethylimidazole	206.5—207.5°C.
14	*o*-chlorobenzaldehyde	2-(*o*-chlorophenyl)-4(5)-trifluoromethylimidazole	165—167°C.
15	*m*-chlorobenzaldehyde	2-(*m*-chlorophenyl)-4(5)-trifluoromethylimidazole	186.5—187.5°C.
16	*p*-chlorobenzaldehyde	2-(*p*-chlorophenyl)-4(5)-trifluoromethylimidazole	226—228°C.
17	3,4-dichlorobenz-aldehyde	2-(3,4-dichlorophenyl)-4(5)-trifluoromethylimidazole	212.5—213.5°C.
18	2,4-dichlorobenz-aldehyde	2-(2,4-dichlorophenyl)-4(5)-trifluoromethylimidazole	191—193°C.
19	*p*-carboxybenzaldehyde	2-(*p*-carboxyphenyl)-4(5)-trifluoromethylimidazole	287°C. dec.

Examples 2—33A (Continued)

Ex. No.	(0.044 mole) Starting Material	Product	Melting Point
20	*p*-methylbenzaldehyde	2-(*p*-methylphenyl)-4(5)-trifluoromethylimidazole	218—220°C.
21	*m*-methylbenzaldehyde	2-(*m*-methylphenyl)-4(5)-trifluoromethylimidazole	190—191°C.
22	*p*-sulfamoylbenzaldehyde	2-(*p*-sulfamoylphenyl)-4(5)-trifluoromethylimidazole	290°C. dec.
23	5-indane carboxaldehyde	2-(5-indanyl)-4(5)-trifluoromethylimidazole	211—213°C.
24	3-cinnoline-carboxaldehyde	2-(3-cinnolyl)-4(5)-trifluoromethylimidazole	275—277°C.
25	benzaldehyde	2-phenyl-4(5)-trifluoromethylimidazole	208—209.5°C.
26	*p*-methoxybenzaldehyde	2-(*p*-methoxyphenyl)-4(5)-trifluoromethylimidazole	204—206°C.
27	*p*-acetylaminobenzaldehyde	2-(*p*-acetylaminophenyl)-4(5)-trifluoromethylimidazole	273—274°C.
28	*p*-nitrobenzaldehyde	2-(*p*-nitrophenyl)-4(5)-trifluoromethylimidazole	195—196.5°C.
29	*p*-dimethylaminobenzaldehyde	2-(*p*-dimethylaminophenyl)-4(5)-trifluoromethylimidazole	264—265°C.
30	3,4-methylenedioxybenzaldehyde	2-(3,4-methylenedioxyphenyl)-4(5)-trifluoromethylimidazole	204—207°C.
31	*m*-bromobenzaldehyde	2-(*m*-bromophenyl)-4(5)-trifluoromethylimidazole	189°C.
32	3-methoxypyrazine-carboxaldehyde	2-[2(5-methoxypyrazinyl)-4-(5)-trifluoromethylimidazole	218—220°C.
33	*p*-isopropylbenzaldehyde	2-(*p*-isopropylphenyl)-4(5)-trifluoromethylimidazole	249°C.
33A	6-quinolinecarboxaldehyde	2-(6-quinolyl)-4(5)-trifluoromethylimidazole	254.5—255°C.

Following the above procedure and starting from the appropriate aldehyde, there are also obtained 2 - benzyl - 4(5) - trifluoromethylimidazole, m.p. 176—177°C; 2 - isobutyl - 4(5) - trifluoromethylimidazole, m.p. 123—125°C; 2 - (4 - methyl - 3 - sulfamoylphenyl) - 4(5) - trifluoromethylimidazole, m.p. 256—257°C; and 2 - (4 - pyridyl - 1 - oxide) - 4(5) - trifluoromethylimidazole, m.p. 244—246°C.

Example 34

2 - (*p* - Aminophenyl) - 4(5) - Trifluoromethylimidazole

2 - (*p* - Acetamidophenyl) - 4(5) - trifluoromethylimidazole (4 grams) is suspended in 10% hydrochloric acid (85 ml.), and the suspension is heated at 100°C. for about 30 minutes. The resulting solution is filtered, and the filtrate is neutralized with aqueous sodium bicarbonate. The crude product settles out of the neutral solution, and after recrystallization from benzene, 2 - (*p* - aminophenyl) - 4(5) - trifluoromethylimidazole, m.p. 214.5—215°C., is obtained.

Example 35

p - [4(5) - Trifluoromethyl - 2 - Imidazolyl] - Maleanilic Acid

2 - (*p* - Aminophenyl) - 4(5) - trifluoromethylimidazole (1.13 grams, 0.005 mole) is dissolved in ether (150 ml.). A solution of maleic anhydride (0.5 grams, 0.005 mole) in ether (50 ml.) is added to the resulting solution, and the resulting solution is allowed to stand for one hour at room temperature. The product settles out of solution and is collected by filtration. Additional crystals are obtained upon concentration of the ether filtrate. The combined solids are dissolved in 2.5% aqueous sodium hydroxide and re-precipitated by the addition of hydrochloric acid. Upon filtration and recrystallization from 70% ethanol, there is obtained *p* - [4(5) - trifluoromethyl - 2 - imidazolyl] - maleanilic acid, m.p. 235.5—237°C.

Example 36

2 - (3,4 - Dimethoxyphenyl) - 4(5) - Trifluoromethylimidazole

Sodium acetate trihydrate (0.084 mole) is dissolved in 50 ml. of water, and 1,1 - dibromo - 3,3,3 - trifluoroacetone (0.042 mole) is added to the resulting aqueous solution. The solution is heated for 25 minutes at 95°C. and is then cooled in an ice bath. The cooled solution is added to a solution of 3,4-dimethoxybenzaldehyde (0.044 mole) in methanol (175 ml.). Concentrated aqueous ammonia (50 ml.) is added to the alcoholic solution, and the reaction mixture is allowed to stand for 5 hours at room temperature. The mixture is then concentrated to about 75 ml., and the product separates from the solution as an oil which solidifies on standing. Upon recrystallization from alcohol, there is obtained 2 - (3,4 - dimethoxyphenyl - 4(5) - trifluoromethylimidazole, m.p. 188—190°C.

When in the above procedure *p* - N,N - dimethylsulfamoylbenzaldehyde and *p*-methylaminobenzaldehyde are used in place of 3,4-dimethoxybenzaldehyde, there are obtained 2 - (*p* - N,N - dimethylsulfamoylphenyl) - 4(5) - trifluoromethylimidazole and 2 - (*p* - methylaminophenyl) - 4(5) - trifluoromethylimidazole, respectively.

Example 37

When in Example 1 2,6 - dimethyl - 4 - pyridinecarboxaldehyde, 4,6 - dimethyl - 2 - pyridinecarboxaldehyde, and 2 - methyl - 3 - pyridinecarboxaldehyde are used in place of 4-pyridinecarboxaldehyde, there are obtained 2 - (2,6 - dimethyl - 4 - pyridyl) - 4(5) - trifluoromethylimidazole, 2 - (4,6 - dimethyl - 2 - pyridyl) - 4(5) - trifluoromethylimidazole, and 2 - (2 - methyl - 3 - pyridyl) - 4(5) - trifluoromethylimidazole, respectively.

Example 38

N - Methyl - 4[4(5) - Trifluoromethyl - 2 - Imidazolyl] - Pyridinium Iodide

To a solution of 2 - (4 - pyridyl) - 4(5) - trifluoromethylimidazole (2.13 grams, 0.01 mole) in methanol (50 ml.) is added methyl iodide (7 grams, 0.05 mole). The resulting solution is allowed to stand for 24 hours at room temperature, and the solvent is concentrated until a solid is obtained. The solid is washed with diethyl ether and is collected by filtration, yielding 2.4 grams of crude product. Upon recrystallization from isopropyl alcohol, N - methyl - 4[4(5) - trifluoromethyl - 2 - imidazolyl] - pyridinium iodide is obtained, m.p. 230—232°C., dec.

When in the above procedure ethyl iodide is used in place of methyl iodide, N - ethyl - 4[4(5) - trifluoromethyl - 2 - imidazolyl] - pyridinium iodide is obtained.

Example 39

2 - (*p* - Fluorophenyl) - 1 - Methyl - 4(And 5) - Trifluoromethylimidazole

Dimethylsulfate (0.63 grams, 0.005 mole) is added to a solution of 2-(*p*-fluorophenyl) - 4(5) - trifluoromethylimidazole (1.1 grams, 0.005 mole) in acetic acid (10 ml.), and the reaction mixture is refluxed overnight. After 17 hours at reflux, additional dimethylsulfate (0.63 grams, 0.005 mole) is added, and the solution is heated at reflux

for an additional 5 hours. The acetic acid is removed *in vacuo*, and the resulting residue is triturated with dilute ammonium hydroxide, water, and then hexane. The hexane extract is concentrated to a solid residue and is sublimed to yield 200 mg. of product. Upon recrystallization from hexane, 2 - (*p* - fluorophenyl) - 1 - methyl - 4 (and 5)-trifluoromethylimidazole are obtained, m.p. 81—84.5°C. Thin-layer chromatography and VPC indicate the presence of two isomeric components.

When in the above procedure diethylsulfate is employed in place of dimethylsulfate, 2 - (*p* - fluorophenyl) - 1 - ethyl - 4 (and 5) - trifluoromethylimidazole are obtained.

Example 40

1 - (2 - Hydroxyethyl) - 5 - Trifluoromethylimidazole

4(5)-Trifluoromethylimidazole (0.062 mole) is dissolved in 150 ml. of acetic acid, and boron trifluoride etherate (0.057 mole) is added to the resulting solution. Ethylene oxide (0.35 mole) in 20 ml. of hexane is added dropwise with stirring during one hour to the reaction mixture while maintaining the temperature of the reaction mixture at 32—35°C. with a water bath. After the addition of ethylene oxide is complete, the mixture is concentrated *in vacuo* to about 20 ml., and the residue is diluted with 50 ml. of water neutralized to pH 7 with aqueous sodium hydroxide and extracted with 100 ml. of ethyl acetate. The extract is dried over magnesium sulfate and filtered. Upon removal of the solvent, 1 - (2 - hydroxyethyl) - 5 - trifluoromethylimidazole is obtained.

When in the above procedure 2 - (*o* - chlorophenyl) - 4(5) - trifluoromethylimidazole and 2 - (*p* - methylphenyl) - 4(5) - trifluoromethylimidazole are used in place of 4(5) - trifluoromethylimidazole, there are obtained 1 - (2 - hydroxyethyl) - 2 - (*o* - chlorophenyl) - 5 - trifluoromethylimidazole and 1 - (2 - hydroxyethyl) - 2 - (*p* - methylphenyl) - 5 - trifluoromethylimidazole, respectively.

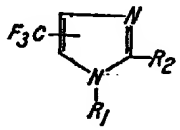
Example 41

2 - Pyrazinyl - 4(5) - Trifluoromethylimidazole

Sodium acetate trihydrate (5.8 grams, 0.042 mole) is dissolved in 20 ml. of water, and 1,1 - dibromo - 3,3,3 - trifluoroacetone (5.8 grams, 0.021 mole) is added to the resulting aqueous solution. The solution is heated for 30 minutes at 100°C. and is then cooled in an ice bath. The cooled solution is added to a solution of 2-pyrazinecarboxaldehyde (2.3 grams, 0.022 mole) in methanol (100 ml.). Concentrated aqueous ammonia (25 ml.) is added to the alcoholic solution, and the reaction mixture is allowed to stand for 5 hours at room temperature. The mixture is then concentrated to about 35 ml., and the product separates from the solution as an oil which solidifies on standing. Upon recrystallization from acetonitrile, there is obtained 2 - pyrazinyl - 4(5) - trifluoromethylimidazole, m.p. 237—238°C.

WHAT WE CLAIM IS:—

1. A compound of the formula



or a non-toxic salt thereof, in which R_1 is a hydrogen atom or a C_{1-5} alkyl or C_{1-5} hydroxyalkyl radical, and R_2 is a hydrogen atom, a C_{1-5} alkyl radical, an aryl or heteroaryl radical said radical optionally having from one to three C_{1-5} alkyl or C_{1-5} alkoxy substituents, a substituted phenyl radical having from one to three of the following substituents, viz. halogen, cyano, carboxy, (C_{1-5} alkoxy) carbonyl, C_{1-5} alkyl, C_{2-5} alkylidene, sulfamoyl, C_{1-5} alkylsulfamoyl, di(C_{1-5} alkyl)sulfamoyl, C_{1-5} alkoxy, C_{2-5} alkanoylamino, nitro, amino, C_{1-5} alkylamino, di(C_{1-5} alkyl)amino, methylenedioxy attached to adjacent carbon atoms of the phenyl residue, a fused alkylene bridge having 3 to 6 carbons and attached to adjacent carbon atoms of the phenyl residue, and a β-carboxyacrylamido group, viz. —NHCOCH=CHCOOH.

2. A compound as claimed in claim 1, in which R_2 is pyridyl and R_1 is hydrogen.

3. A compound as claimed in claim 1, in which R_2 is quinolyl and R_1 is hydrogen.

4. A compound as claimed in claim 2, in which R_2 is 4-pyridyl.

5. A compound as claimed in claim 3, in which R_2 is 6-quinolyl.

6. The process that comprises reacting a 1,1 - dihalo- 3,3,3 - trifluoroacetone compound with a base and then reacting the resulting mixture with ammonia and an aldehyde of formula R_2CHO, where R_2 is as defined in claim 1 except that it is not an amino-substituted phenyl residue, to produce a compound as claimed in claim 1 in which R_1 is hydrogen and R_2 is as defined in claim 1 except that it is not an amino-substituted phenyl residue.

7. A process as claimed in claim 6 in which the reaction between the 1,1 - dihalo - 3,3,3 - trifluoroacetone compound and base is carried out at a temperature of 80—100°C.

8. A process as claimed in claim 6 or 7 in which 1,1 - dibromo - 3,3,3 - trifluoroacetone is reacted with sodium acetate at 80—100°C and the resulting mixture, after being cooled, is reacted with pyridinecarboxaldehyde and ammonia.

9. A process as claimed in claim 6 or 7 in which 1,1 - dibromo - 3,3,3 - trifluoroacetone is reacted with sodium acetate at 80—100°C and the resulting mixture, after being cooled, is reacted with quinolinecarboxaldehyde and ammonia.

10. A process according to claim 6 or 7 in which R_2 contains a nitro substituent, including the further step of reducing the nitro to an amino substituent.

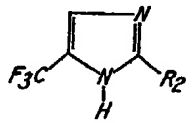
11. A process as claimed in claim 6 or 7 in which R_2 contains an alkanoylamino substituent, including the further step of hydrolysing the latter to an amino substituent.

12. A process according to any one of claims 6—11, including the further step of reacting the resulting 2 - substituted - 4(5) - trifluoromethyl compound with an alkylating agent or a C_{2-5} 1,2- or 1,3- epoxy alkane in the presence of a Lewis acid to produce a compound as claimed in claim 1 in which R_1 is C_{1-5} alkyl or C_{2-5} hydroxy alkyl, and R_2 is as defined in claim 1.

13. A process as claimed in claim 12 in which the carboxaldehyde is 4-pyridinecarboxaldehyde.

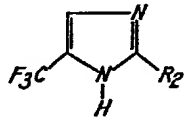
14. A process as claimed in claim 12 in which the carboxaldehyde is 6-quinolinecarboxaldehyde.

15. The process that comprises reacting a compound of the formula:



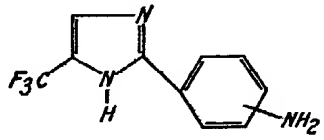
in which R_2 is as defined in claim 1, with an alkylating agent, to produce a compound as claimed in claim 1 in which R_1 is C_{1-5} alkyl.

16. The process that comprises reacting a compound of the formula:

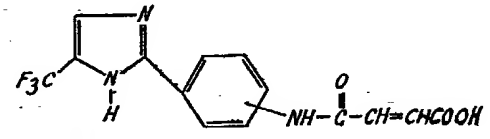


in which R_2 is as defined in claim 1 with a Lewis acid and a C_{2-5} epoxy alkane to produce a compound as claimed in claim 1 in which R_1 is C_{2-5} hydroxy alkyl.

17. The process that comprises reacting a compound of the formula:



with maleic anhydride to produce a compound of the formula:



18. A process as claimed in claim 6, substantially as hereinbefore described in any one of Examples 1—33A, 36 and 37.

19. A process as claimed in claim 15, substantially as hereinbefore described in Example 38 or 39.

20. A process as claimed in claim 16, substantially as hereinbefore described in Example 40.

21. A process as claimed in claim 17, substantially as hereinbefore described in Example 35.

22. A process as claimed in claim 11, in which the alkanoylamino substituent is hydrolysed substantially as hereinbefore described in Example 34.

23. A compound as claimed in claim 1, when prepared by a process as claimed in any one of claims 6—22 or an obvious chemical equivalent of such a process.

24. Each and every compound as claimed in claim 1 hereinbefore individually specified, with the exception of those claimed in claims 4 and 5.

25. A composition useful in the treatment of gout that comprises a pharmaceutically acceptable diluent, carrier or coating together with a compound as claimed in any one of claims 1 to 3, 23 and 24 as the active ingredient.

26. A composition as claimed in claim 25, in which the active ingredient is 2 - (4 - pyridyl) - 4(5) - trifluoromethylimidazole.

27. A composition as claimed in claim 25, in which the active ingredient is 2 - (6 - quinolyl) - 4(5) - trifluoromethylimidazole.

28. A composition as claimed in any one of claims 25 to 27 in the form of a tablet.

29. A composition as claimed in any one of claims 25 to 27 in the form of a capsule.

30. A composition as claimed in any one of claims 25 to 27 in the form of a syrup.

31. A composition as claimed in any one of claims 25 to 27 in the form of a pill.

32. A composition as claimed in any one of claims 25 to 27 in the form of an elixir.

33. A composition as claimed in claim 25, substantially as hereinbefore described in Formulation I, II or III.

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